March 8, 2013

DATE 3/18/13
SB 296

The Honorable David Howard, Chairman House Human Services Committee Montana House of Representatives PO Box 200400 Helena, MT 59620-0400

RE: SB 296 ESTABLISHING THAT PHYSICIANS MAY NOT BE DISCIPLINED FOR TREATING LYME DISEASE WITH LONG-TERM ANTIBIOTICS

Dear Chairman Howard and Members of the House Human Services Committee:

Please accept this letter on behalf of the below signed members of the Montana Infectious Disease (ID) Network in opposition of SB 296. The ID Network is a strategic statewide collaborative and its membership includes the ID physicians currently practicing in Montana. The ID Network's vision is to serve as an advising regional, clinical, and readiness partner in the area of infectious and communicable disease. In that capacity, the ID Network has actively been working to ensure the consistent use of recommended and evidence-based strategies to treat infectious diseases.

The Infectious Disease Society of America provided clinical guidelines (*The Clinical Assessment, Treatment and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America*) for the treatment of Lyme disease. The guidelines are intended for use by health care providers who care for patients with Lyme disease. The guidelines were published in 2006 set forward both the doses and durations of antimicrobial therapy recommended for the treatment of Lyme disease. In 2009 the guidelines were reviewed following a legal challenge and found to be scientifically and medically justified. The results of this review were published and state that "prospective, controlled clinical trials for extended antibiotic treatment of Lyme disease have demonstrated considerable risk of harm, including potential lifethreatening adverse events."

These guidelines are evidence based and provide the gold standard for Lyme disease treatment. SB 296 is not consistent with these guidelines and therefore puts the health of patients at risk. We oppose SB 296 as this bill does not support the appropriate treatment guidelines for Lyme disease. We urge you to vote no to SB 296.

Sincerely,

Ray Geyer, DO – Great Falls Clinic, Great Falls

Mark Winton, MD – Bozeman Deaconess Hospital, Bozeman

Fred Kahn, MD – St. Vincent Healthcare, Billings

Les Whitney, MD – Community Medical Center, Missoula

Don Skillman, MD – St. Peters Hospital, Helena

Claude Tonnerre, MD – St. Patrick Hospital, Missoula

George Risi, MD – Infectious Disease Specialists PC, Missoula

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The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

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Evidence-based guidelines for the management of patients with Lyme disease, human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis), and babesiosis were prepared by an expert panel of the Infectious Diseases Society of America. These updated guidelines replace the previous treatment guidelines published in 2000 (Clin Infect Dis 2000; 31[Suppl 1]:1-14). The guidelines are intended for use by health care providers who care for patients who either have these infections or may be at risk for them. For each of these Ixodes tickborne infections, information is provided about prevention, epidemiology, clinical manifestations, diagnosis, and treatment. Tables list the doses and durations of antimicrobial therapy recommended for treatment and prevention of Lyme disease and provide a partial list of therapies to be avoided. A definition of post-Lyme disease syndrome is proposed.

EXECUTIVE SUMMARY

Background

Lyme disease is the most common tickborne infection in both North America and Europe. In the United

States, Lyme disease is caused by Borrelia burgdorferi, which is transmitted by the bite of the tick species Ixodes scapularis and Ixodes pacificus. Clinical manifestations most often involve the skin, joints, nervous system, and heart. Extracutaneous manifestations are less commonly seen than in earlier years. Early cutaneous infection with B. burgdorferi is called erythema migrans, which is the most common clinical manifestation of Lyme disease. I. scapularis may also be infected with and transmit Anaplasma phagocytophilum (previously referred to as Ehrlichia phagocytophila) and/or Babesia microti, the primary cause of babesiosis. Thus, a bite from an I. scapularis tick may lead to the development of Lyme disease, human granulocytic anaplasmosis (HGA, formerly known as human granulocytic ehrlichiosis), or babesiosis as a single infection or, less frequently, as a coinfection. Clinical findings are sufficient

Clinical Infectious Diseases 2006; 43:1089-134

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Received 21 August 2006; accepted 21 August 2006; electronically published 2 October 2006.

These guidelines were developed and issued on behalf of the Infectious Diseases Society of America.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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because of the good clinical response with orally administered antibiotics (even in the presence of CSF pleocytosis) and the absence of evidence of recurrent CNS disease in these patients. There was agreement that lumbar puncture is indicated for those in whom there is strong clinical suspicion of CNS involvement (e.g., severe or prolonged headache or nuchal rigidity). Patients with normal CSF examination findings and those for whom CSF examination is deemed unnecessary because of lack of clinical signs of meningitis may be treated with a 14-day course (range, 14–21 days) of the same antibiotics used for patients with erythema migrans (see above) (B-III). Those with both clinical and laboratory evidence of CNS involvement should be treated with regimens effective for Lyme meningitis, as described above (B-III).

Lyme carditis. Patients with atrioventricular heart block and/or myopericarditis associated with early Lyme disease may be treated with either oral or parenteral antibiotic therapy for 14 days (range, 14–21 days). Hospitalization and continuous monitoring are advisable for symptomatic patients, such as those with syncope, dyspnea, or chest pain. It is also recommended for patients with second- or third-degree atrioventricular block, as well as for those with first-degree heart block when the PR interval is prolonged to ≥30 milliseconds, because the degree of block may fluctuate and worsen very rapidly in such patients.

A parenteral antibiotic, such as ceftriaxone, is recommended as initial treatment of hospitalized patients (see recommendations for treatment of Lyme meningitis above) (B-III). For patients with advanced heart block, a temporary pacemaker may be required; expert consultation with a cardiologist is recommended. Use of the pacemaker may be discontinued when the advanced heart block has resolved. An oral antibiotic treatment regimen should be used for completion of therapy and for outpatients, as is used for patients with erythema migrans without carditis (see above) (B-III).

Borrelial lymphocytoma. Available data indicate that borrelial lymphocytoma may be treated with the same regimens used to treat patients with erythema migrans (see above) (B-II).

Pregnancy. Pregnant and lactating patients may be treated in a fashion identical to nonpregnant patients with the same disease manifestation, except that doxycycline should be avoided (B-III).

Late Lyme Disease

Lyme arthritis. Lyme arthritis can usually be treated successfully with antimicrobial agents administered orally. Doxycycline (100 mg twice per day) (B-I), amoxicillin (500 mg 3 times per day) (B-I), or cefuroxime axetil (500 mg twice per day) (B-III) for 28 days is recommended for adult patients without clinical evidence of neurologic disease. For children, amoxicillin (50 mg/kg per day in 3 divided doses [maximum]

of 500 mg per dose]) (B-I), cefuroxime axetil (30 mg/kg per day in 2 divided doses [maximum of 500 mg per dose]) (B-III), or, if the patient is \geq 8 years of age, doxycycline (4 mg/kg per day in 2 divided doses [maximum of 100 mg per dose]) (B-I) is recommended. Oral antibiotics are easier to administer than intravenous antibiotics, are associated with fewer serious complications, and are considerably less expensive. However, it is important to recognize that a small number of patients treated with oral agents have subsequently manifested overt neuroborreliosis, which may require intravenous therapy with a β -lactam antibiotic (see the paragraph below) for successful resolution. Further controlled trials are needed to compare the safety and efficacy of oral versus intravenous therapy for Lyme arthritis.

Neurologic evaluation that may include lumbar puncture should be performed for patients in whom there is a clinical suspicion of neurologic involvement. Adult patients with arthritis and objective evidence of neurologic disease should receive parenteral therapy with ceftriaxone (A-II) for 2-4 weeks. Cefotaxime or penicillin G administered parenterally is an acceptable alternative (B-II). For children, intravenous ceftriaxone or intravenous cefotaxime is recommended (B-III); penicillin G administered intravenously is an alternative (B-III). See the recommendations above for treatment of patients with Lyme meningitis for suggested doses of each of these antimicrobials.

For patients who have persistent or recurrent joint swelling after a recommended course of oral antibiotic therapy, we recommend re-treatment with another 4-week course of oral antibiotics or with a 2-4-week course of ceftriaxone IV (B-III) (for dosages of oral agents, see the recommendations above for treatment of erythema migrans, and for dosages of parenteral agents, see the recommendations above for treatment of Lyme meningitis). A second 4-week course of oral antibiotic therapy is favored by panel members for the patient whose arthritis has substantively improved but has not yet completely resolved, reserving intravenous antibiotic therapy for those patients whose arthritis failed to improve at all or worsened. Clinicians should consider waiting several months before initiating retreatment with antimicrobial agents because of the anticipated slow resolution of inflammation after treatment. If patients have no resolution of arthritis despite intravenous therapy and if PCR results for a sample of synovial fluid (and synovial tissue if available) are negative, symptomatic treatment is recommended (B-III). Symptomatic therapy might consist of nonsteroidal anti-inflammatory agents, intra-articular injections of corticosteroids, or disease-modifying antirheumatic drugs (DMARDs), such as hydroxychloroquine; expert consultation with a rheumatologist is recommended. If persistent synovitis is associated with significant pain or limitation of function,

arthroscopic synovectomy may reduce the duration of joint inflammation (B-II).

Late neurologic Lyme disease. Adult patients with late neurologic disease affecting the central or peripheral nervous system should be treated with intravenous ceftriaxone for 2 to 4 weeks (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-II). Response to treatment is usually slow and may be incomplete. Re-treatment is not recommended unless relapse is shown by reliable objective measures. Ceftriaxone is also recommended for children with late neurologic Lyme disease (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-III). See the recommendations above on the treatment of Lyme meningitis for suggested doses of each of these antimicrobials.

Acrodermatitis chronica atrophicans. Available data indicate that acrodermatitis chronica atrophicans may be treated with a 21-day course of the same antibiotics (doxycycline [B-II], amoxicillin [B-II], and cefuroxime axetil [B-III]) used to treat patients with erythema migrans (see above). A controlled study is warranted to compare oral with parenteral antibiotic therapy for the treatment of acrodermatitis chronica atrophicans.

Coinfection. Coinfection with B. microti or A. phagocyto-philum or both may occur in patients with early Lyme disease (usually in patients with erythema migrans) in geographic areas where these pathogens are endemic. Coinfection should be considered in patients who present with more-severe initial symptoms than are commonly observed with Lyme disease alone, especially in those who have high-grade fever for >48 h, despite receiving antibiotic therapy appropriate for Lyme disease, or who have unexplained leukopenia, thrombocytopenia, or anemia (A-III). Coinfection might also be considered in the situation in which there has been resolution of the erythema migrans skin lesion but either no improvement or worsening of viral infection—like symptoms (B-III).

Post-Lyme Disease Syndromes

There is no well-accepted definition of post–Lyme disease syndrome. This has contributed to confusion and controversy and to a lack of firm data on its incidence, prevalence, and pathogenesis. In an attempt to provide a framework for future research on this subject and to reduce diagnostic ambiguity in study populations, a definition for post–Lyme disease syndrome is proposed in these guidelines. Whatever definition is eventually adopted, having once had objective evidence of *B. burgdorferi* infection must be a condition sine qua non. Furthermore, when laboratory testing is done to support the original diagnosis of Lyme disease, it is essential that it be performed by well-qualified and reputable laboratories that use recommended and appropriately validated testing methods and interpretive criteria. Unvalidated test methods (such as urine an-

tigen tests or blood microscopy for *Borrelia* species) should not be used.

There is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease. Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (≥6 months) subjective symptoms after recommended treatment regimens for Lyme disease (E-I).

Therapeutic modalities not recommended. Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient, the following are not recommended for treatment of patients with any manifestation of Lyme disease: first-generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine penicillin G, combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not others), long-term antibiotic therapy, anti-Bartonella therapies, hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide, specific nutritional supplements, and others (see table 4) (E-III).

HGA

All symptomatic patients suspected of having HGA should be treated with antimicrobial therapy because of the risk of complications (A-III). Suspicion of HGA is based on the acute onset of unexplained fever, chills, and headache, often in association with thrombocytopenia, leukopenia, and/or increased liver enzyme levels in patients with exposure to I. scapularis or I. pacificus ticks within the prior 3 weeks. Confirmation of the diagnosis is based on laboratory testing (see the HGA section of the text), but antibiotic therapy should not be delayed in a patient with a suggestive clinical presentation pending the results. Identification of the characteristic intragranulocytic inclusions on blood smear is the most rapid diagnostic method, but such inclusions are often scant in number or sometimes absent; in addition, other types of inclusions unrelated to HGA or overlying platelets can be misinterpreted by inexperienced observers. Testing for antibodies to A. phagocytophilum is the most sensitive diagnostic method, but only if a convalescentphase serum sample is assayed.

Doxycycline is recommended as the treatment of choice for patients who are suspected of having symptomatic HGA (A-II). The dosage regimen for adults is 100 mg given twice per day by mouth (or intravenously for those patients unable to take an oral medication) for 10 days. This treatment regimen should be adequate therapy for patients with HGA alone and for patients who have coinfection with *B. burgdorferi*. Persistence of fever for >48 h after initiation of doxycycline treatment

Final Report of the Lyme Disease Review Panel of the Infectious Diseases Society of America (IDSA)

INTRODUCTION AND PURPOSE

In November 2006, the Connecticut Attorney General (CAG), Richard Blumenthal, initiated an antitrust investigation to determine whether the Infectious Diseases Society of America (IDSA) violated antitrust laws in the promulgation of the IDSA's 2006 Lyme disease guidelines, entitled "The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America" (the 2006 Lyme Guidelines). IDSA maintained that it had developed the 2006 Lyme disease guidelines based on a proper review of the medical/scientific studies and evidence by a panel of experts in the prevention, diagnosis, and treatment of Lyme disease. In April 2008, the CAG and the IDSA reached an agreement to end the investigation. Under the Agreement and its attached Action Plan, the 2006 Lyme Guidelines remain in effect, and the Society agreed to convene a Review Panel whose task would be to determine whether or not the 2006 Lyme Guidelines were based on sound medical/scientific evidence and whether or not these guidelines required change or revision.

The Review Panel was not charged with updating or rewriting the 2006 Lyme Guidelines. Any recommendation for update or revision to the 2006 Lyme Guidelines would be conducted by a separate IDSA group.

This document is the Final Report of the Review Panel.

REVIEW PANEL MEMBERS

Carol J. Baker, MD, Review Panel Chair Baylor College of Medicine Houston, TX

William A. Charini, MD Lawrence General Hospital, Lawrence, MA

Paul H. Duray, MD¹ (retired) Westwood, MA

Paul M. Lantos, MD
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¹ Dr. Duray resigned from the Panel on October 7, 2009, due to family illness.

Post Lyme Syndromes

2006 Recommendation

There is no well-accepted definition of post–Lyme disease syndrome. This has contributed to confusion and controversy and to a lack of firm data on its incidence, prevalence, and pathogenesis. In an attempt to provide a framework for future research on this subject and to reduce diagnostic ambiguity in study populations, a definition for post–Lyme disease syndrome is proposed in these guidelines. Whatever definition is eventually adopted, having once had objective evidence of *B. burgdorferi* infection must be a condition sine qua non. Furthermore, when laboratory testing is done to support the original diagnosis of Lyme disease, it is essential that it be performed by well-qualified and reputable laboratories that use recommended and appropriately validated testing methods and interpretive criteria. Unvalidated test methods (such as urine antigen tests or blood microscopy for *Borrelia* species) should not be used.

Panel Determination/Discussion - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that the sentence that begins with "Whatever definition" be modified as follows: "Whatever definition is eventually adopted, having once had objective clinical or laboratory evidence of *B. burgdorferi* infection must be a condition sine qua non until a syndrome is formally defined."

2006 Recommendation

To date, there is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease.

Panel Determination/Discussion - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (7-1).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that consideration be given to changing the phrase "no convincing biologic evidence" to something more specific, such as "Reports purporting to show the persistence of viable B. burgdorferi organisms after treatment with recommended regimens for Lyme disease have not been conclusive or corroborated by controlled studies:" It has been proposed by some that there are hardy, drug-tolerant reservoirs of B. burgdorferi, including intracellular cystic forms. To date, this has not been shown to correlate with symptom persistence, nor has eradication of these forms been shown to correlate with symptom improvement.

2006 Recommendation

Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (>6 months) subjective symptoms after recommended treatment regimens for Lyme disease (E-I).

Panel Determination/Discussion - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

The Review Panel reviewed numerous sources of evidence for this contentious topic. These included but were not limited to: 1) a large volume of case reports and case series submitted by representatives of the International Lyme and Associated Diseases Society (ILADS) and referenced by that society's published guidelines; 2) case reports cited by representatives of ILADS and patient representatives in oral presentations to the Panel during the Hearing on July 30, 2009; 3) journal correspondence published in response to several Lyme disease practice guidelines, editorials, and clinical trials; 4) patient testimony; and 5) the available placebo-controlled randomized clinical trials of long-term antibiotic therapy for symptoms attributed to Lyme disease.

Upon reviewing this abundance of material, and after lengthy discussions among the Review Panel members, the Review Panel reached the following conclusions:

1. The prospective, controlled clinical trials for extended antibiotic treatment of Lyme disease have demonstrated considerable risk of harm, including potentially life-threatening adverse events. Such events include intravenous catheter infection, including septicemia (line sepsis), venous thromboembolism, drug hypersensitivity reactions, and drug-induced cholecystitis. Minor adverse events, such as diarrhea and candidiasis, were also more common in antibiotic-treated patients [286, 438, 459, 493, 666]. In a recent cohort of 200 patients, catheter-associated adverse events such as thrombosis and infection occurred on average 81 days into therapy, underscoring the cumulative risk of adverse events with increasing time [895].

In clinical trials evaluating prolonged IV antibiotics for Lyme disease, there has been a lower rate of line sepsis in patients receiving IV ceftriaxone than those receiving IV placebo. It must be emphasized however, this adverse event is directly related to the intravenous access device. As ceftriaxone is intrinsically inactive against many common causes of line sepsis, including *Enterococcus, Candida, methicillin-resistant Staphylococcus aureus* (MRSA), and coagulase-negative *Staphylococci*, it should not be seen as mitigating the potential risk of septicemia due to long term intravenous lines.

- 2. Prospective, controlled clinical trials have demonstrated little benefit from prolonged antibiotic therapy. Nearly all primary outcome measures have failed to demonstrate a benefit to prolonged antibiotic therapy. Statistically significant improvements in treatment groups were not demonstrated across studies, were nonspecific, were of unclear clinical importance, and in one case, not sustained at the end of the trial [286, 438, 459, 493, 666].
- 3. The risk/benefit ratio from prolonged antibiotic therapy strongly discourages prolonged antibiotic courses for Lyme disease. Several presenters in the July 30th hearing argued that patients with symptoms attributed to chronic Lyme disease confer considerable societal cost. This argument, however, was not accompanied by quantitative evidence from controlled trials that prolonged antibiotic therapy could even partly reduce this cost. The Panel concluded that a societal benefit was at best hypothetical based on current evidence.

It has been argued that prolonged parenteral antibiotics are considered sufficiently safe for their routine use in such infections as osteomyelitis and endocarditis [895]. The Panel does not agree with this comparison, however, because in these

conditions clinical trials have decisively shown a clinical and mortality benefit. On the other hand, in the case of Lyme disease, there has yet to be a single high quality clinical study that demonstrates comparable benefit to prolonging antibiotic therapy beyond one month. Therefore, the Review Panel concluded that in the case of Lyme disease inherent risks of long-term antibiotic therapy were not justified by clinical benefit.

This conclusion was reached despite the large volume of case reports, case series, anecdotes, and patient testimonials reviewed that attested to perceived clinical improvement during antibiotic therapy. Such evidence is by its nature uncontrolled and highly subject to selection and reporting biases. In many published case reports patients did not receive initial Lyme disease therapy consistent with the current standard of care, so it was impossible to be sure that shorter duration therapy had failed. In some cases the diagnosis of Lyme disease was doubtful based on clinical presentations consistent with other illnesses. Some patients were abnormal hosts and not representative of the general population. Many reports included patients whose diagnosis was made before the implementation of the CDC recommendation for 2-tier serological testing, and were therefore based on less stringent criteria. Finally, caution should be used in extrapolating results from European studies to North American patients, due to the well-established microbiological and clinical distinctions in Lyme borreliosis on the two continents.

In the end, such sources of evidence were felt to be fertile material for hypothesisgeneration, but intrinsically incapable of hypothesis-testing. By contrast, the prospective, randomized, controlled trials were formal hypothesis tests with strict recruitment criteria, prospectively defined outcome measures, and independent oversight.

The Panel's conclusions, which are consistent with those reached by guidelines panels from the IDSA as well as other societies, represent the state of medical science at the time of writing. Only high-quality, prospective, controlled clinical trial data demonstrating both benefit and safety will be sufficient to change the current recommendations.

HGA

2006 Recommendation

All symptomatic patients suspected of having HGA should be treated with antimicrobial therapy because of the risk of complications (A-III). Suspicion of HGA is based on the acute onset of unexplained fever, chills, and headache, often in association with thrombocytopenia, leukopenia, and/or increased liver enzyme levels in patients with exposure to *I. scapularis* or *I. pacificus* ticks within the prior 3 weeks. Confirmation of the diagnosis is based on laboratory testing (see the HGA section of the text), but antibiotic therapy should not be delayed in a patient with a suggestive clinical presentation pending the results. Identification of the characteristic intragranulocytic inclusions on blood smear is the most rapid diagnostic method, but such inclusions are often scant in number or sometimes absent; in addition, other types of inclusions unrelated to HGA or overlying platelets can be misinterpreted by inexperienced observers. Testing for antibodies to *A. phagocytophilum* is the most sensitive diagnostic method, but only if a convalescent-phase serum sample is assayed.